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## SINGLE DOSE PHARMACOKINETICS OF EFAVIRENZ IN HEALTHY INDIAN SUBJECTS

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### Abstract

**Background & Objective:** Access to antiretroviral therapy in India is improving. Efavirenz (EFV) is a commonly used non-nucleoside reverse transcriptase inhibitor used to treat HIV infection. No information is available on the pharmacokinetics of EFV in Indian subjects. The aim of this study was to obtain information on single dose pharmacokinetics of efavirenz (EFV) in healthy Indian subjects.

**Methods:** Sixteen adult healthy volunteers (8 males and 8 females) were administered a single oral tablet of 600 mg EFV after an overnight fast. Blood samples were collected at 1, 2, 3, 4, 5, 6, 10, 24 and 48 hours post dosing. Plasma EFV concentrations were estimated by HPLC, and certain pharmacokinetic variables were calculated.

**Results:** Plasma EFV concentrations were higher in females than males at all the time points, the differences being significant at 1 ( $p<0.001$ ) and 2 ( $p=0.05$ ) hours. Females had significantly higher peak concentration ( $C_{max}$ ) of EFV than males ( $p=0.05$ ) (3.11 & 1.90  $\mu\text{g/ml}$ ). The inter-individual variability in  $C_{max}$  and  $AUC_{0-48}$  were 42 and 45% respectively.

**Conclusions:** This study provides basic information on the pharmacokinetics of EFV in Indian subjects. Females had higher peak levels of EFV than males. Inter-subject variability was high. Further studies are necessary to describe the pharmacokinetic profile of EFV under steady state conditions in Indian patients on antiretroviral treatment.

**Key words:** Efavirenz, HIV infection, pharmacokinetics, Indian subjects

### Introduction

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor widely used in the treatment of HIV infection because of its robust antiviral efficacy and relatively good pharmacokinetic and safety

profile.<sup>1,2</sup> Current recommendations include EFV in many first-line regimens.<sup>2,3</sup> Variability in response to antiretroviral therapy has been attributed to differences in virologic, immunologic, pharmacologic, and behavioral characteristics.<sup>4</sup> Significant inter-patient variability in the kinetics of antiretroviral drugs has been reported.<sup>5,6</sup> Variability in absorption and disposition of EFV may partially explain the heterogeneity of response to treatment<sup>7</sup>. Some studies have shown a relationship between low and high EFV plasma levels and treatment failure and CNS side effects respectively.<sup>8</sup> Therefore, elucidation of the pharmacokinetic profile of EFV and its variability provides a relevant component of HIV therapeutic optimization.

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India has a large number of HIV-positive individuals and access to antiretroviral therapy is improving. With increasing number of patients on treatment, it is important to study the pharmacokinetics of commonly used antiretroviral drugs. In addition, differences in EFV pharmacokinetics between various racial / ethnic groups,<sup>9-15</sup> and between males and females<sup>11, 15, 16</sup> have been reported. No information is available on the pharmacokinetics of EFV in Indian subjects, who receive treatment with generic drugs, and who could have genetic differences in the cytochrome P-450 system. We, therefore carried out a study to obtain basic information on the pharmacokinetics of EFV in healthy Indian subjects, following administration of a single dose of 600mg of the drug, which is the conventional dose used to treat HIV-1 infected patients. This would give us an idea about the blood levels of EFV that may be expected in patients who receive treatment with this drug.

## Methods

### Participants

Sixteen healthy volunteers aged 18 years and above, comprising of 8 males and 8 females took part in the study. All the volunteers were from Tamil Nadu, South India and belonged to the same ethnic group. They underwent physical examination by a medical officer. None of the volunteers was suffering from any illness or taking concurrent medications at the time of the study. The purpose of the study was explained to the study participants and only those willing to participate were included. Informed written consent was obtained from all the study participants before they took part in the study. Smokers, chronic alcoholics and females on hormonal birth control pills were not included in the study.

### Drug administration and sample collection

All the volunteers were requested to report to the clinic division of the Tuberculosis Research Centre, Chennai, in the morning after an overnight fast. On the day of the study, about five ml. of blood was collected (0 hour) in a heparinized container. A single tablet of 600 mg EFV (Viranz, Ranbaxy, India) was administered and blood samples (5 ml.) were collected at 1, 2, 3, 4, 5, 6, 10, 24 and 48 hours after drug administration. The total volume of blood collected from each volunteer during the study period was about 50 ml. All blood draws were made from the cephalic vein using an indwelling catheter with

heparin lock. Breakfast and lunch were provided at two and six hours of drug administration. The blood samples were centrifuged immediately, plasma separated and stored at  $-20^{\circ}\text{C}$  until assay, which was carried out within four days.

### Assay Procedure

Plasma EFV concentrations were determined by high performance liquid chromatography (HPLC) (Shimadzu Corporation, Kyoto, Japan) according to the method of Langmann *et al.*,<sup>17</sup> using UV detection set at 246 nm. Efavirenz was extracted into the organic solvent, and the contents were centrifuged at 2500rpm for 10 minutes at ambient temperature. The organic layer was evaporated to dryness, dried residue reconstituted in the mobile phase and injected into the HPLC column. Nefazodone was used as an internal standard. The mobile phase was a mixture of potassium dihydrogen orthophosphate and acetonitrile. The retention times of the internal standard and EFV were 1.8 and 5.8 minutes respectively. Unknown concentrations were derived from linear regression analysis of the peak height ratios (EFV / internal standard) vs. concentration curve. The assay was linear from 0.0625 to 10.0  $\mu\text{g/ml}$  with a correlation coefficient value of 0.9992 and limit of quantification of 0.05  $\mu\text{g/ml}$ . The intra- and inter-day coefficients of variation were 3.8 and 4.6% respectively, and recovery of EFV from human plasma was 98%.

### Pharmacokinetic analysis

On each series of plasma EFV concentrations, certain pharmacokinetic variables were calculated. Maximum concentrations ( $C_{\text{max}}$ ) and the time to attain  $C_{\text{max}}$  ( $T_{\text{max}}$ ) were determined by direct visual inspection of data. EFV concentration-time data were analyzed by a non-compartmental model using WinNonlin software (Version 5.0.1) (Pharsight Corporation, Mountain View, CA, USA). The log trapezoidal rule was used to compute the exposure or area under the time concentration curve from 0 to 48 hours ( $\text{AUC}_{0-48}$ ). Elimination rate constant ( $\lambda$ ) was calculated by applying log-linear regression. This was used to extrapolate AUC to infinity. The apparent oral clearance (Cl) was calculated as dose/ $\text{AUC}_{0-\infty}$ . Half-life ( $t_{1/2}$ ) was calculated by dividing 0.693 by  $\lambda$ , and volume of distribution ( $V_d$ ) by dividing Cl by  $\lambda$ .

## Statistical evaluation

Data were expressed as Median (Range). The significance of differences in the pharmacokinetic parameters between males and females was evaluated by Mann-Whitney 'U' test. A p value of  $\leq 0.05$  was considered statistically significant. Correlation between body weight and that of  $C_{max}$  and  $AUC_{0-48}$  &  $AUC_{0-\infty}$  were tested using Spearman's rank correlation test.

## Results

The details of the study participants are given in table 1. Male and female volunteers were similar with respect to age, body weight and dose of EFV normalized to body weight. Plasma EFV concentrations were higher in females than in males at all the time-points tested (Figure 1), the differences being significant at 1 ( $p < 0.001$ ) and 2 ( $p = 0.05$ ) hours. Certain pharmacokinetic variables calculated based on plasma EFV concentrations in male and female volunteers are given in Table 2. Females had a significantly higher  $C_{max}$  than males ( $p = 0.05$ ), the median values being 3.11 and 1.90  $\mu\text{g/ml}$

respectively. Mean  $C_{max}$  values after normalising to body weight in males and females were 0.036 and 0.055  $\mu\text{g/ml}$ ; this difference was also significant ( $p = 0.05$ ). Although  $AUC_{0-48}$  &  $AUC_{0-\infty}$  and CI were higher and lower respectively in females than in males, these differences were not statistically significant. Overall, the inter-subject variability in  $C_{max}$  and  $AUC_{0-48}$  was 42 and 45% respectively. There was a negative correlation between body weight and that of  $C_{max}$  and  $AUC_{0-48}$  &  $AUC_{0-\infty}$ , but these correlations were not significant.

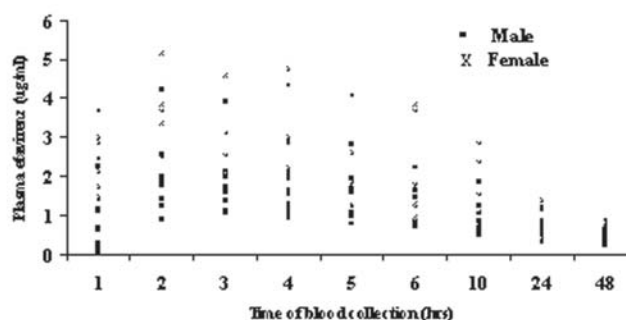


Figure 1 Plasma efavirenz concentration in males (n=8) & females (n=8) at different times points

Table 1 Basic characteristics of study participants

Characteristics	Median (Range)	
	Males (n=8)	Females (n=8)
Age (years)	31(25-52)	35(26-47)
Body weight (kg)	65(53-75)	60(48-65)
EFV dose /kg body weight	9.2(8.0-11.3)	10.0(9.2-12.5)

Table 2 Single dose pharmacokinetics of efavirenz (600 mg) in healthy subjects

Pharmacokinetic Variables	Median (Range)		
	Males (n=8)	Females (n=8)	Overall (n=16)
Peak concentration ( $\mu\text{g/ml}$ )*	1.90 (1.41-4.21)	3.11 (1.93-5.15)	2.34 (1.41-5.15)
Time to attain peak concentration (hours)	2.00 (2-4)	2.00 (1-3)	2.00 (1-4)
Exposure $_{0-t}$ ( $\mu\text{g/ml}$ . hours)	35.91(20.66-58.89)	47.62 (27.04-88.76)	39.9 (20.66-88.76)
Exposure $_{0-\infty}$ ( $\mu\text{g/ml}$ . hours)	64.24 (32.08-100.31)	94.59 (44.72-131.19)	68.36 (32.08-131.19)
Apparent oral clearance (litres/min)	9.53 (5.98-18.7)	6.65 (4.47-13.62)	8.78 (4.47-18.7)
Half-life (hours)	31.77 (23.53-71.71)	41.98 (22.26-74.4)	35.77 (22.26-74.4)
Volume of Distribution(liters)	589.66 (251.56-969.95)	455.09 (167.39-765.46)	525.7 (167.39-969.95)

\* denotes  $p = 0.05$



## Discussion

Presently, there are no data available on EFV pharmacokinetics in Indian subjects. This study presents data on certain pharmacokinetic variables of EFV obtained in healthy volunteers, who were administered a single dose of 600 mg EFV. Although considerable data on steady state pharmacokinetics of EFV are available in other populations, there are not many reports available on single dose pharmacokinetics of this drug at a dose of 600 mg. The Sustiva™ product monograph reports a  $C_{max}$  of 0.5 to 2.9 µg/ml for single oral doses ranging from 100-1600mg in uninfected volunteers<sup>18</sup>. Since these values correspond to a wide dose range, a direct comparison of these values with this study data (Table 2) cannot be made. However, it appears that the median  $C_{max}$  of 2.34 µg/ml obtained in this study is on the higher side than that reported earlier.<sup>18</sup> Also a  $T_{max}$  of 2 hours observed in this study is lower than the earlier report, which implies that the absorption of EFV in the Indian subjects was relatively rapid. Single dose pharmacokinetic data of EFV reported by Reddy *et al*<sup>19</sup> from nine HIV-infected individuals were 2.7 µg/ml, 3.5 hours and 29.97 µg/ml.hours (median) respectively for  $C_{max}$ ,  $T_{max}$  and  $AUC_{0-24}$ . A qualitative comparison of this data with that of our study shows that  $C_{max}$  values are almost similar, but  $T_{max}$  is shorter in Indian subjects. The AUC values could not be compared since the time periods were different (24 and 48 hours). However, an  $AUC_{0-48}$  value of 39.90 µg/ml.hours obtained in our study appears to be higher, given the fact that concentrations of EFV beyond 24 hours were very low. Hence a higher exposure to EFV, and thereby a lower clearance of the drug could be expected in Indian patients infected with HIV. Barrett *et al*<sup>11</sup> have also predicted a lower clearance of EFV in Asians and Africans relative to Caucasians.

Recently, several studies have found that sex can have a modest influence on the pharmacokinetic profile of certain antiretroviral drugs. Potentially sex-specific influences, such as endogenous or exogenous hormones, could impact antiretroviral tolerance, and influence how women respond and react to anti-retroviral. A few observational studies have described a higher frequency of antiretroviral-related adverse effects among women compared to

men.<sup>20,21</sup> Sex-related differences in pharmacokinetics of EFV have been reported, with females having 20% higher exposure than males.<sup>15, 16</sup> A lower clearance of EFV in females relative to males has also been reported.<sup>11</sup> Burger *et al*<sup>15</sup> have observed that gender is an important factor in determining variability in plasma EFV concentrations, and they have suggested that one needs to be alert for signs of EFV-induced toxicity in females. A higher  $C_{max}$  (even after normalizing to body weight) in females than in males as observed in this study could have implications for patient management, in terms of adverse event profiles. The mechanism for sex-related differences in the pharmacokinetics of EFV, or antiretroviral drugs in general is not clear. It has been suggested that this could be due to the fact that females weigh less and have smaller volumes compared to males. However, in this study, despite normalizing  $C_{max}$  to body weight, we still observed a difference between females and males.

Pharmacokinetic differences between patients are an important factor leading to variability in response to antiretroviral agents<sup>6, 22</sup>. High inter-patient variability in EFV pharmacokinetics related to CYP-dependent metabolism and P-glycoprotein-dependent intestinal secretion,<sup>8</sup> and its potential relationship with markers of efficacy and toxicity have been reported.<sup>7, 15</sup> The high inter-subject variability in  $C_{max}$  and AUC observed in this study point to the fact that monitoring of plasma concentrations of EFV (therapeutic drug monitoring) may be useful in certain situations.

Efavirenz undergoes metabolism predominantly through CYP2B6. Genetic variability of CYP2B6, in different populations has been reported.<sup>12-14</sup> Variation in CYP2B6 expression among different ethnic groups has also been reported.<sup>12</sup> Race as an important factor in determining inter-individual variability in plasma EFV concentrations has been reported<sup>15</sup>. There are reports of differences in EFV pharmacokinetics a result of single nucleotide polymorphisms in the CYP2B6 gene.<sup>9-11</sup> A 3-fold higher plasma EFV levels in African-Americans than European-Americans has been attributed to a CYP2B6 allelic variant (G516T) that commonly occurs in the black population. This single nucleotide polymorphism was responsible for a lower rate of clearance of EFV in the African-Americans than European-Americans, rendering the former group

more susceptible to CNS side effects.<sup>9</sup> A novel specific CYP2B6 allele (T983C) in Africans has been shown to cause impaired metabolism of EFV.<sup>14</sup>

In the absence of EFV pharmacokinetic data in Indian subjects, this study provides preliminary information on plasma levels that may be expected in patients. A limitation of the study was inadequate sampling time points used to estimate plasma EFV kinetics. Due to the prolonged half-life of EFV, it would have been ideal to estimate drug levels up to 360 hours. However, in this study, due to logistic reasons, we could not collect blood samples after 48 hours. Generally, pharmacokinetics of drugs could change in disease states, and it is not easy to extrapolate the pharmacokinetic parameters from healthy subjects to patients. Hence pharmacokinetic studies of EFV in HIV-infected patients on antiretroviral treatment in India are required. This would enable us to examine relationships between EFV pharmacokinetics, efficacy and CNS toxicity. Further studies are also necessary to determine whether genetic polymorphisms in drug metabolizing enzymes, particularly CYP2B6 influence EFV disposition in this population. It would also be worth exploring sex-related differences in tolerability and adverse reactions among patients, as there is some suggestion from our study that females have higher peak and drug exposure levels of EFV.

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## References

1. Joly V, Yeni P. Non-nucleoside reverse transcriptase inhibitors. *AIDS Rev* 1999; 1:37-44.
2. Staszewski S, et al – Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; 341: 1865-73.
3. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. The panel on clinical practices for treatment of HIV infection. 2003. Available at <http://www.aidsinfo.nih.gov/guidelines>
4. Brundage AC, Yong FH, Fenton T et al. Inpatient variability of efavirenz concentrations as a predictor of virologic response to antiretroviral therapy. *Antimicrob Agents Chemother*. 2004; 48:979-84.
5. Regazzi MB, Villani P, Maserati R. Pharmacokinetic variability and strategy for therapeutic drug monitoring of saquinavir in HIV-1 infected individuals. *Br J Pharmacol* 1999; 47: 379-82.
6. Fletcher CV. Pharmacologic considerations for therapeutic success with antiretroviral agents. *Ann Pharmacol*. 1999; 33: 989-95.
7. Csajka C, Marzolini C, Fattinger K, et al. Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection. *Clin Pharmacol Ther* 2003; 73: 20-30.
8. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; 15: 71-5.
9. Haas DW, Ribaud HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004; 18: 2391-400.
10. Ribaud HJ, Clifford DB, Gulick RM, et al. Relationships between efavirenz

- pharmacokinetics, side effects, drug discontinuation, virologic response and race: results from ACTG A5095/A5097s. In: Program and abstracts of the 11<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, 2004 (Abstract 132).
11. Barrett JS, Joshi AS, Chai M et al. Population pharmacokinetic meta-analysis with efavirenz. *Int J Clin Pharmacol Ther*. 2002; 40: 507-19.
  12. Lamba V, Lamba J, Yasuda K, et al. Hepatic CYP2B6 expression: Gender and ethnic differences and relationship to CYP2B6 genotype and CAR (Constitutive Androstane Receptor) expression. *J Pharmacol Exp Ther* 2003; 307: 906-22.
  13. Klein K, Lang T, Saussele T, et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. *Pharmacogenet Genomics* 2005; 15: 861-73.
  14. Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific CYP2B6 allele in Africans causing metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics* 2006; 16: 191-8.
  15. Burger D, van der Heiden I, la Porte C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. *Br J Clin Pharmacol* 2006; 61: 148-54.
  16. Phair JP, Becker SL. Integrating pharmacokinetics into treatment decisions: Strategies for optimal patient care. In: *iMed Options*, North Western University, Feinberg School of Medicine 2004.
  17. Langmann P, Schirmer D, Vath T, et al. High performance liquid chromatographic method for the determination of HIV-1 non-nucleoside inhibitor efavirenz in plasma of patients during highly active antiretroviral therapy. *J Chromatogr B Biomed Sci Appl*. 2001; 755: 151-6.
  18. DuPont Pharmaceuticals Company. Sustiva<sup>TM</sup> (efavirenz capsules). (1998) Prescribing information: Available at: <http://www.sustiva.com>
  19. Reddy YS, Gotzkowsky SK, Eron JJ, et al. Pharmacokinetic and pharmacodynamic investigation of efavirenz in the semen and blood of human immunodeficiency virus type 1 –infected men. *J Infect Dis* 2002; 186: 1339-43.
  20. Clark R. Sex differences in antiretroviral therapy – associated intolerance and adverse events. *Drug Saf*. 2005; 28: 1075-83.
  21. Van Leth F, Andrews S, Grinsztejn B, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. *AIDS* 2005; 19: 463-71.
  22. Hirsch MS, Brunn-Vezinet F, D'Aquila RT, Hammer SM, Johnson VA, Kuritzkes DL, Loveday C, Mellors JW, Clotet B, Conway B, Demeter LM, Vella S, Jacobsen DM, Richman DD.
  23. Antiretroviral drug testing in adult HIV-1 infection: recommendations of an International AIDS society-USA panel. *JAMA* 2000; 283: 2417-26